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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,733	11/20/2001	Avi J. Ashkenazi	P2730P1C68	9890

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,733	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-124,129-131 and 135-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-124,129-131 and 135-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 07 December 2004 has been entered in full. Claims 125-128, 132-134 were cancelled. Claims 119-124, 129-131 and 135-138 are under examination.

The Declaration of Avi Ashkenazi under 37 CFR1.132, filed 07 December 2004, has been entered.

The Declaration of Audrey D. Goddard under 37 CFR1.132, filed 07 December 2004, has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection to claims 119-123 and 132-138 under 35 U.S.C. 112, first paragraph, written description, as set forth at pages 9-11 of the previous Office Action (29 June 2004), is *withdrawn* in view of the amendment (07 December 2004).

The rejection to claims 119-125, 127, 128, 132-138 under 35 U.S.C. 112, second paragraph, as set forth at pages 11-12 of the previous Office Action (29 June 2004), is *withdrawn* in view of the amendment (07 December 2004).

The rejection to claims 119-123 and 132-138 under 35 U.S.C. 102(b) as being anticipated by Hillier *et al.* Locus/Accession Number AA464988 (10 June 1997), as set

forth at pages 12-13 of the previous Office Action (29 June 2004), is *withdrawn* in view of the amendment (07 December 2004).

The rejection to claims 119-122 and 132-134 under 35 U.S.C. 102(e) as being anticipated by Bandman *et al.,* US Patent 6,183,968 B1, as set forth at pages 13-14 of the previous Office Action (29 June 2004), is *withdrawn* in view of the amendment (07 December 2004).

The rejection of claims 119-123 and 135-138 under 35 U.S.C. 103(a) as being unpatentable over Hillier *et al.* Locus/Accession Number AA464988 in view of Gerald *et al.*, US Patent No. 5,989,834, as set forth at page 14 of the previous Office Action (29 June 2004), is *withdrawn* in view of the amendment (07 December 2004).

The rejection of claims 119-122 and 132-138 under 35 U.S.C. 103(a) as being unpatentable over Bandman *et al.,* US Patent No. 6,183,968 B1 in view of Gerald *et al.,* US Patent No. 5,989,834, as set forth at page 15 of the previous Office Action (29 June 2004), is *withdrawn* in view of the amendment (07 December 2004).

Claim Rejections - 35 USC § 101

Claims 119-124, 129-131, and 135-138 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established. The basis for this rejection is set forth at pages 2-7 of the previous Office Action (29 June 2004).

Applicant argues that the Examiner acknowledged that the nucleic acids encoding PRO1187 showed a positive correlation to lung cancer. Applicant cites the

Utility Examination Guidelines 66 Fed. Reg. 1092 (2001), MPEP 2107 II (B) and the Revised Interim Utility Guidelines Training Materials, 1999. In reply to the Examiner's citation of Haynes, Konopka and Pennica, Applicant states that the claimed utility for the PRO1187 nucleic acids is based on its use in the diagnosis of lung cancer and is not based on structural similarity to known proteins. Applicant states that they rely on the gene amplification date for patentable utility of this case.

Applicant's arguments have been fully considered but not deemed persuasive. Firstly, the Examiner "reiterated" what the instant specification teaches. The Examiner did not "acknowledge" that the nucleic acid encoding PRO1187 showed a positive correlation for lung cancer (see previous Office Action 29 June 2004, page 3, last paragraph). The previous claims did not have a biological function or activity associated with the claimed nucleic acid. The closest information regarding the instant invention was a proposal in the specification that the cDNA clone (DNA62876-1517) encoded a polypeptide having sequence identity with endo-beta-1,4-xylanase. The Examiner cited Karp and Skolnick to demonstrate that function could not be based on similarity to known proteins.

Applicant describes Example 170 (specification, page 539). Applicant states that the results of TaqMan PCR are reported in deltaCt units. Applicant states that one unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control. Applicant argues that Table 9C indicates that PRO1187 showed approximately 1.17-1.55 deltaCt units, which corresponds to 2.25 to 2.928-fold amplification in squamous cell carcinomas of lung. Applicant argues that the Goddard declaration

submits that 2-fold amplification is considered significant and thus the PRO1187 gene has utility as a diagnostic marker for lung cancer.

The Declaration of Audrey D. Goddard under 37 CFR 1.132 filed 07 December 2004 is insufficient to overcome the rejection of claims 119-124, 129-131, 135-138 based upon 35 U.S.C. 101 as set forth in the last Office action. Applicant's arguments regarding TaqMan PCR are not deemed persuasive because it only shows that the instant specification provides an invitation to experiment, and not a readily available utility. The PRO1187 gene *has not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1187 nucleic acid was amplified in lung cancer, to a minor degree (about 2.5-3.0 fold). No mutation or translocation of PRO1187 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1187 is expressed in corresponding normal tissues, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1187 is amplified in lung cancer samples, and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica *et al.,* the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Furthermore, the Declaration does not provide data such that the Examiner can independently draw conclusions. Only Dr. Goddard's conclusions are provided in the declaration. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The Examiner submits Hu *et al.* (2003, Journal of Proteome Research 2:405-412) to demonstrate this. Hu *et al.* analyzed 2286 genes that showed a greater than a 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

In response to the Examiner's rejection that there is a lack of correction of gene amplification data based on aneuploidy, Applicant submits that aneuploid tissue are cancerous or precancerous. Applicant argues that the present invention is directed to nucleic acid useful in the detection of cancer, irrespective of the mechanism by which gene amplification occurs. Applicant argues that even if the presence of aneuploid cells or tissues were to predict a propensity towards cancer, the instant nucleic acids are still useful as diagnostic tools. Applicant submits a declaration by Dr. Ashkenazi. Dr. Ashkenazi states, "An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy". "It is important to

understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy". "As long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes." Dr. Ashkenazi states that if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. Dr. Ashkenazi argues that if a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

The Declaration of Avi Ashkenazi under 37 CFR 1.132 filed 07 December 2004 is insufficient to overcome the rejection of claims 123, 124, 129-131, 135-138 based upon 35 U.S.C. 101 as set forth in the last Office action. Applicant's arguments are not found persuasive because aneuploidy can occur in damaged/abnormal, but not necessarily cancerous cells, for example Down's syndrome cells. Thus the mechanism by which gene amplification occurs is very important. It is very relevant if the signal originates from an abnormal number of chromosomes. Dr. Ashkenazi discussion regarding various scenarios of how increased copy number of a gene can have utility in the absence of over-expression of the corresponding gene product is not found persuasive because a significant difference in the cancer samples relative to normal tissue was not detected for the claimed nucleic acid.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First paragraph, Enablement

Claims 119-124, 129-131, and 135-138 remain rejected under 35 U.S.C. 112, first paragraph, enablement. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth at pages 7-9 of the previous Office Action (29 June 2004).

Applicant incorporates their response to the rejection under 35 USC 101 in response to the rejection under 35 USC 112, first paragraph. Applicants arguments have been fully considered but are not found to persuasive for the reasons discussed above in the maintained rejection in 35 USC 101.

Furthermore, the claims are still drawn to polynucleotides having at least 80%, 85%, 90%, 95% or 99% sequence identity with SEQ ID NO:398. The Examiner maintains that there is no guidance in the specification or working examples showing what variant sequence is overexpressed in those specific tumors. If one skilled in the art were to make probes from the claimed variants, there is no guidance (or working examples) regarding what changes can be made without loss of probe specificity. In addition, the art fails to teach what variant sequences are amplified in various tumors.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Priority

Priority of the instant application is denied because the priority does not meet the requirements of 35 USC 112, First Paragraph. Therefore, the effective filing date for the purposes of applying art is the same as the actual filing date. This decision was set forth at page 12 of the previous Office Action (29 June 2004).

Applicant states that they rely on the gene amplification assay for patentable utility, which was first disclosed in U.S. Provisional Application 60/141,037, filed June 23, 1999, priority to which has been claimed in this application. Applicant contends that they should be entitled to at least an effective filing date of June 23, 1999.

Applicant's arguments have been fully considered but not deemed persuasive. The gene amplification assay relied upon in this application may have been disclosed in the provisional application, but it does not remedy the utility and enablement rejection to the instant claims. Because the instant claims lack utility and enablement, priority is granted only to the instant filing date.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
2/10/05

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER